

**REMARKS**

Claims 87 and 96 are objected to for the reasons noted in the official action. The above requested claim amendments are believed to overcome all of the raised informalities concerning the claims. If any further amendment to the claims is believed necessary, the Examiner is invited to contact the undersigned representative of the Applicant to discuss the same.

Next, claims 87-99 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons noted in the official action. The rejected claims are accordingly amended, by the above claim amendments, and in accordance with the following remarks, the presently pending claims are now believed to particularly point out and distinctly claim the subject matter regarded as the invention, thereby overcoming all of the raised § 112, second paragraph, rejections.

The Examiner indicates that Applicant's specification intends for the boundary layer to be a rigid layer so as to constrict and maintain the shape of the developing tissue, like a mold. The Applicant agrees that the boundary layer maintains a predetermined shape and size of the human body part to be replaced as it conforms to the construct of the porous support structure. As discussed in the specification at least at paragraph 031:

For a defined cell culture chamber to be provided in the interior of the support structure 1 for the cells 2, and for the size and shape of the implant to be formed to be maintained, it is necessary to ensure that the outer wall of the support structure 1 is impermeable to cells.

It is not that the boundary layer is, or is not, "rigid", but that it is impermeable to cells. In other words, whether or not the boundary layer is rigid, what is explicit in the specification is that the boundary layer *maintains* the predetermined shape i.e. predetermined by the body part to be replaced, throughout the claimed process in order to produce a specifically shaped and sized implant.

In accordance with the Examiner's concern as to the criticality of this aspect of the present invention, the Applicant has amended steps a) and e) to more fully clarify this aspect of the present invention. In this regard, step a) recites the step of, "forming an inert material into a porous support structure having a predetermined shape and size corresponding to and substantially maintaining the predetermined shape and size of the human body part to be replaced:". In other words, as explicitly and described and understood from the specification, the predetermined shape and size of the human body part to be replicated is maintained throughout the entire process. That this desired shape and size is maintained is further confirmed in step e) which recites the step, "removing the boundary layer after completion of the cell formation process, thereby producing the implantable tissue construct which corresponds to the predetermined shape and size of the human body part to be replaced." Thus, whether or not the boundary layer is "rigid", what is critical is that the size and shape of the desired body part to be replicated is clearly defined by constraining the cell growth as closely as possible

In view of these amendments, the Applicant believes that the claims are now more distinctly defined to have the specific size and shape retaining properties to which the Examiner refers to on page three of the official action. If the Examiner does not agree with the above amendments and remarks, the Applicant is certainly willing to consider any other amendments to clarify this aspect of the present invention which the Examiner might suggest. In this regard, the Applicant respectfully requests the Examiner to telephone the undersigned attorney of record to discuss the same for entering such amendments by way of an Examiner's Amendment, if appropriate.

Claims 87-90, 92 and 94 are rejected, under 35 U.S.C. § 103, as being unpatentable over Bader '282. The Applicant acknowledges and respectfully traverses the raised obviousness rejection in view of the above amendments and the following remarks.

The Examiner's rejection ostensibly requests that the Applicant further differentiate the structure of the present invention from that of Bader '282. In this regard, the above discussed amendments to claim 87 are believed to more clearly differentiate the present invention from Bader '282 which as noted in the previous office actions is a cell carrier having a variable chamber volume as determined by the elastic membrane or film. Furthermore, Applicant has amended step b) to include the feature wherein the boundary layer is applied to the porous support structure in such a manner so as to substantially conform to the predetermined size and shape as described in step a). This step is not disclosed, taught or suggested in any manner by Bader '282 which merely notes that an extra cellular matrix can be placed in the interior of a cell chamber 11A.

Step b) is important because it goes beyond the structural differences of the present invention and speaks specifically to the novel method claimed by the present invention. In the instant claims the method steps recite that first the support structure (extra cellular matrix, ECM) is formed into the desired, or predetermined shape or form, and subsequently the boundary layer material is applied to this shape. In claim 87, "a) forming an inert material into a porous support structure having a predetermined shape and size corresponding to and substantially maintaining the predetermined shape and size of the human body part to be replaced; b) encapsulating the entire porous support structure by means of a boundary layer of cell-impermeable material substantially conforming to the predetermined shape and size of the porous support structure;" Obviously, one cannot encapsulate the support structure until it is formed and therefore this aspect of the present invention is entirely opposite of the method disclosed in Bader '282.

Bader '282 discloses merely the known carrier plates and frames and cover plates which predefine the "space" or interior into which the ECM is placed. Bader '282 specifically discusses at page 11 lines 10-14, "...a type of network structure or an extracellular matrix can be placed

in the interior in order to improve the result." The very nature and structure of the design in Bader ensures that the cell culture chamber is first defined by the boundary of the frame, cover plate and carrier plate, and then the extracellular matrix, if any, is inserted or placed within the cell culture chamber. Such a step as presently claimed by the Applicant is not possible with such known structures. In fact entirely opposite from the presently claimed method, in the applied reference any extracellular matrix introduced into the cell culture chamber will have to be defined by the shape of the cell culture chamber.

Having a clear understanding of the method of the present invention leads to further clarification of the differences between the structures disclosed in the reference and the presently claimed invention. The main issue here is what the Applicant believes is a misdescription of the presently claimed invention in the Official Action which describes at page 6, last paragraph, "...the instant claims utilize a bioreactor that comprises a porous support structure encompassed within a boundary layer material, wherein culture medium exists *between* the porous support structure and the boundary layer material;" This may be the design of the reference as shown for example in Figs. 2 and 3 of Bader '282, but contrary to the Examiner's statement that the two bioreactors are identical on page 7 of the official action, in the presently claimed invention where the shape of the support structure defines the cell culture chamber the cells are supported *within* the support structure, and not between the support structure and the flexible film as shown in the cited reference.

Steps b) and c) of claim 87 clarify this aspect of the present invention where, in step "b) encapsulating the entire porous support structure by means of a boundary layer of cell-impermeable material substantially *conforming* to the predetermined shape and size of the porous support structure; c) introducing living cells into the porous support structure which constitutes a cell culture chamber;" Nowhere in the cited Bader '282 reference is there any disclosure, teaching or suggestion relating to the film or boundary layer conforming to the

extracellular matrix, and while it may be that in Bader `282 the cells are introduced "between" the extracellular matrix and the boundary, this is not the case in the presently claimed invention where the boundary layer conforms to the support structure and the cells must therefore be within the support structure itself defining the cell culture chamber.

Regarding the assertions on page 9 that "...Bader teaches the extracellular matrix (porous support structure) can approximate the size and shape of a desired tissue, for example, bone, hear valve or bladder..." the Applicant notes that this paragraph of Bader `282 relates explicitly to the carrier plate, or carrier portion for the cells, and not the extracellular matrix, having a shape for a heart valve or bladder. In fact, contrary to the further assumption in this paragraph of the official action that "...it is inherently required that an initial step comprise forming the extracellular matrix into the desired shape and size." , at page 14 lines 31-33 Bader discloses, "[i]n this way, the cells are provided in practice with a mold into which a connective tissue matrix or collagen matrix with cells is then injected." Thus, not only is the claimed method not inherent, but the cited disclosure in fact, teaches specifically away from the Applicant's presently claimed method of initially forming the underlying support structure into the desired predetermined shape.

Also, with respect to the assumption that Bader `282 teaches inoculating the cells onto the extracellular matrix via inflow and outflow lines, the Applicant believes that the disclosure here is also misdescribed in reference to the presently claimed method and structure. Lines 25- 27 state, "[i]n a first step, the matrix of the collagen is prepared externally. The matrix or the collagen is then injected into the cell culture chamber11a. Again, this disclosure is completely opposite of the presently claimed invention. Futhermore, lines 27-30 require "The structures or the cell culture chamber. 11a can be either already coated with the cells, or the cells 11 are injected directly together with the collagen or with the matrix." This simultaneous injection, does not introduce the cells into the chamber through and inflow and outflow as

claimed after the formation of the support structure and boundary layers of the present invention. Also, this description cannot be taken in context with that of page 5 lines 13-27 which details nothing in regards to the introduction of cells or the extracellular matrix via the inflow and outflow where it is described merely how nutrients are provided to the structure. Thus, the Applicant believes that the present invention is not only not rendered obvious by the Bader `282 reference but that the above noted portions of the disclosure actually teach directly away from the specifically recited method of claim 87.

The Applicant thanks the Examiner for indicating that claim 96 is apparently allowable given the above section 112 1<sup>st</sup> paragraph amendments. In addition, the Applicant has added new claims 113-123 as dependent upon claim 96 and which correspond to pending claims 88-95 and 97-100 as currently amended.

If any further amendment to this application is believed necessary to advance prosecution and place this case in allowable form, the Examiner is courteously solicited to contact the undersigned representative of the Applicant to discuss the same.

In view of the above amendments and remarks, it is respectfully submitted that all of the raised obvious rejections should be withdrawn at this time. If the Examiner disagrees with the Applicant's view concerning the withdrawal of the outstanding rejection(s) or applicability of the Bader `282 reference, the Applicant respectfully requests the Examiner to indicate the specific passage or passages, or the drawing or drawings, which contain the necessary teaching, suggestion and/or disclosure required by case law. As such teaching, suggestion and/or disclosure is not present in the applied references, the raised rejection should be withdrawn at this time. Alternatively, if the Examiner is relying on his/her expertise in this field, the Applicant respectfully requests the Examiner to enter an affidavit substantiating the Examiner's position so that suitable contradictory evidence can be entered in this case by the Applicant.

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In view of the foregoing, it is respectfully submitted that the raised rejection(s) should be withdrawn and this application is now placed in a condition for allowance. Action to that end, in the form of an early Notice of Allowance, is courteously solicited by the Applicant at this time.

The Applicant respectfully requests that any outstanding objection(s) or requirement(s), as to the form of this application, be held in abeyance until allowable subject matter is indicated for this case.

In the event that there are any fee deficiencies or additional fees are payable, please charge the same or credit any overpayment to our Deposit Account (Account No. 04-0213).

Respectfully submitted,



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